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REVIEW

Emerging Biological Therapies in Severe Eosinophilic Asthma

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ABSTRACT

A small fraction of patients with asthma have severe, persistent disease that is often refractory to standard therapy. To meet this need, a growing emphasis has been placed on the development of alternative, novel therapies and the ability to characterize those patients who are most likely to benefit from these therapies. The eosinophil has been identified as a primary mediator in airway inflammation and as a potential pharmacological target. This narrative review outlines the need for more phenotype-directed therapies in severe asthma, and discusses the supporting evidence for monoclonal antibodies directed against key pro-eosinophilic T-helper 2 (Th2) inflammatory cytokines as additive agents in the treatment of severe asthma with an eosinophilic phenotype.

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INTRODUCTION

Asthma affects 25.7 million people worldwide, and is associated with a significant healthcare and economic burden to patients and society [1]. Three to ten percent of adults diagnosed with asthma are believed to suffer from severe, refractory disease [2, 3]. A single exacerbation requiring urgent intervention can increase the annual treatment costs by as much as threefold [4], and recurrent exacerbations have been shown to result in a progressive loss of lung function in some patients [5]. Up to 30% of adults with severe asthma will require oral corticosteroids in addition to inhaled corticosteroids to maintain control [6–8].

There is a need to identify those patients who are most at risk for exacerbations and to characterize the potential treatment options that might reduce these risks [9]. It has been suggested that within this group of patients, detailed phenotyping or characterizing based on readily observable traits [10] using clinical

symptoms, markers of inflammation, and lung function might be useful [3, 9, 11]. Although there is no widely agreed upon phenotypic classification scheme, most proposed groupings include an early-atopic or allergic group, a delayed-onset group (often involving obese patients with a female predominance), and a late-onset, eosinophilic predominant group [3, 10–12], as shown in Table 1. However, in asthma, each phenotype does not necessarily yield a distinct endotype or subgroup defined by pathogenetic mechanisms of disease at a more cellular level [10]. This consensus has shifted the current research focus towards differentiating the pathobiologic mechanisms of each group so that targeted therapies can be developed.

Recurrent exacerbations are a major contributor to asthma-related morbidity in

Table 1 Phenotypes of asthma [8, 12, 13, 25, 71, 72]

Phenotype	Clinical characteristics	Histology/pathology	Targets	Biologic therapies
Allergic/atopic	Early onset	Eosinophils	Anti-IgE	Omalizumab
	Allergen-driven	Mast cells	Anti-IL-5	Mepolizumab
	Rhinitis ± eczema	IgE receptors	Anti-IL-4	Reslizumab
				Benralizumab[a]
				Dupilumab[a]
Persistent eosinophilic (non-atopic)	Late (20–40 years) onset	Eosinophils	Anti-IL-5	Mepolizumab
	Severe disease		Corticosteroids	Reslizumab
	Severe obstruction		Anti-Th2	Benralizumab[a]
Non-eosinophilic	Late onset	Neutrophils	Steroid-resistant	
	Female predominance	Innate response	Possible role for macrolides	
	Obese			
	Bacterial colonization			
	Severe obstruction			
Allergic bronchopulmonary mycosis (ABPM)	Adult onset	Type 1 hypersensitivity	Corticosteroids	Omalizumab
		Fungus-specific IgE and IgG	Antifungals	
			Possible role for anti-IgE	
Aspirin-intolerant (possible subtype of persistent eosinophilic)	Late onset	Eosinophils	NSAID avoidance	
	Female predominance		Corticosteroids	
	Nasal polyps		LTRA	

Asthma phenotypes are continually evolving as the relationships between biological characteristics and endotypes change. This table includes examples of some of the most commonly accepted phenotypes

LTRA leukotriene receptor antagonist

[a] Investigational therapy

many patients, and seem to predominate in a subgroup with eosinophilic airway inflammation [9, 13]. Although inhaled corticosteroids are effective at reducing airway eosinophilia, up to 50% of patients with severe asthma will have persistent eosinophilia despite treatment [14, 15], suggesting that selective targeting of airway eosinophilia may have benefit.

The purpose of this narrative review is to illustrate both the importance of eosinophilic inflammation in the airway as a distinct subtype of severe asthma, and to review the biologic therapies that are under investigation to specifically treat this patient population. This article is based on previously conducted studies (see Table 2), and does not involve any new studies of human or animal subjects performed by any of the authors.

ROLE OF EOSINOPHILS

Eosinophils have been shown to promote airway inflammation and remodeling in asthma [16], and elevated peripheral blood eosinophil counts have been identified as an independent risk factor for asthma exacerbations [17–20]. Additionally, a reduction in sputum eosinophil count in those patients with moderate to severe asthma has been shown to reduce exacerbations [21–23] and hospital admissions [21]. T-helper type 2 (Th2) lymphocytes are thought to play a key role in the pathogenesis of asthma [24], with an increased serum immunoglobulin E (IgE) and elevated peripheral blood eosinophil count defining the classic phenotype [25]. Blockade of the key Th2 cytokines interleukins-4, -5, and -13 (IL-4, IL-5, and IL-13) is a plausible target for the development of biologic therapies for patients with asthma who remain uncontrolled on conventional therapies.

MEPOLIZUMAB

Interleukin-5 (IL-5) is a pro-inflammatory cytokine released predominantly by helper T cells that stimulates maturation [26] and activation of eosinophils [27], making it a logical target to reduce eosinophil-driven inflammation. Mepolizumab is a humanized monoclonal antibody against IL-5 that prevents the binding of IL-5 to the receptor complex on the surface of the eosinophil [28]. It selectively inhibits eosinophilic inflammation [29–32] and reduces the numbers of eosinophils in the blood and sputum [31, 33–37]. In an early phase-two, double-blinded, randomized, placebo-controlled trial of adults with moderately severe asthma with persistent symptoms despite inhaled corticosteroid therapy [33], Flood-Page and colleagues evaluated the potential benefit of mepolizumab as add-on therapy. While no clinically significant benefit was noted in the treatment arm, the study did demonstrate safety of administration and a nonsignificant trend towards reduced frequency of exacerbations despite a short three-month study period. Additionally, it confirmed mepolizumab's ability to markedly reduce peripheral blood and sputum eosinophils, raising the important question that perhaps with more careful phenotyping, mepolizumab would be more beneficial.

Subsequent clinical studies of mepolizumab began to better elucidate the relevant phenotype in which this agent might be effective. In 2009, Haldar et al. compared mepolizumab versus placebo in the treatment of refractory eosinophilic asthma [34]. The study population included 61 adult patients who met the American Thoracic Society definition of refractory asthma [38], evidence of eosinophilic inflammation in sputum

Table 2 Primary outcomes of randomized controlled trials

Trial	Study population	Size (number of subjects)	Duration (weeks)	Primary outcome	Results
Mepolizumab					
Flood-Page AJRCCM 2007 [33]	Additive therapy to adults with moderate persistent asthma on high-dose ICS	362	12 study period, 8 follow-up (20 total)	Change in morning peak expiratory flow at weeks 12 and 20	Improved peak expiratory flow, reduction in blood eosinophils
Haldar NEJM 2009 [34]	Adults with severe persistent asthma and sputum eosinophil ≥3% despite high-dose ICS or daily oral steroid	61	50	Number of severe exacerbations	Reduction in total number and rate of exacerbations, improved AQLQ score, reduction in sputum and blood eosinophil counts
Nair NEJM 2009 [35]	Adults requiring oral maintenance oral corticosteroids and ICS with persistent sputum eosinophilia (≥3% cells)	20	26	Proportion of patients with exacerbations and % mean reduction in prednisone dose	Reduction in total exacerbations and mean prednisone dose, longer time to first exacerbation, reduction in sputum and blood eosinophils, improvement in JACQ score
Pavord Lancet 2012 [36]	Adolescents and adults on high-dose ICS and additional controller. Subjects must have either ≥3% sputum eosinophils, ≥300 cells/μL blood eosinophils, or FeNo ≥50 ppb	621	52, dose ranging	Annual rate of exacerbation	Reduction in annual rate of exacerbation and blood eosinophil counts
Bel NEJM 2014 [41]	Adults requiring at least 6 months maintenance oral corticosteroids with peripheral blood eosinophils ≥300 cells/μL	135	20 study period, 4 follow-up (24 total)	Percent reduction in daily oral glucocorticoids	Mean 50% reduction in prednisone, reduction in rate of exacerbation, improvement in ACQ-5 and SGRQ scores, reduction in blood eosinophil counts

Table 2 continued

Trial	Study population	Size (number of subjects)	Duration (weeks)	Primary outcome	Results
Ortega NEJM 2014 [37]	Adolescents and adults on high-dose ICS and additional controller with peripheral blood eosinophils ≥150 cells/μL during screening or 300 cells/μL in the previous year	576	32 study period, 8 follow-up (40 total)	Annual rate of exacerbation	Reduction in annual rate of exacerbation, improvement in FEV1, improvement in ACQ-5 and SGRQ scores
Reslizumab					
Castro AJRCCM 2011 [46]	Adults with induced sputum ≥3% eosinophils and ACQ score ≥1.5 despite high-dose ICS plus an additional controller	106	15	Change in ACQ-7 score	Improvement in FEV1 and FVC, reduction in peripheral blood and sputum eosinophil counts, but no clinically significant change in ACQ-7 score
Castro Lancet 2015 [48]	Adolescents and adults with ACQ-7 score ≥1.5 and peripheral blood eosinophil count ≥400 cells/μL despite moderate-dose ICS with or without an additional controller agent	2 duplicate trials, 953 patients	52	Annual rate of exacerbation	Reduction in annual rate of exacerbation, improvement in baseline FEV1, AQLQ score, ACQ-7 score, reduction in peripheral blood eosinophil counts
Bjermer Chest 2016 [49]	Ages 12–75 with ACQ-7 score ≥1.5, airway reversibility, and peripheral blood eosinophil count ≥400 cells/μL despite moderate-dose ICS with or without an additional controller agent	315	16	Change in FEV1	Improvement in FEV1, FVC, and $FEF_{25–75\%}$, improvement in AQLQ score, reduction in SABA use, reduction in blood eosinophil counts

Table 2 continued

Trial	Study population	Size (number of subjects)	Duration (weeks)	Primary outcome	Results
Corren Chest 2016 [50]	Adults with ACQ-7 score ≥1.5 despite moderate-dose ICS with or without an additional controller agent; no selection based on eosinophils	492	16 study period, 12 follow-up (28 total)	Change in FEV1	No change in FEV1, FVC, ACQ score, or SABA use. Subgroup analysis showed improvement in FEV1 compared to placebo in patients with peripheral blood eosinophil count ≥400 cells/μL
Benralizumab					
Nowak AJEM 2015 [56]	Adults presenting in acute exacerbation to an emergency department; not responsive to two inhaled bronchodilator treatments	110 randomized, 72 analyzed per protocol analysis	24 follow-up	Proportion of patients with at least 1 additional exacerbation at week 12	No change in number of exacerbations, FEV1, ACQ score, or AQLQ score; reduction in eosinophil counts
Castro Lancet 2014 [57]	Adults on moderate-dose ICS and LABA ≥12 months with 2–6 exacerbations in the previous year and ACQ-6 score ≥1.5	609	52, dose ranging	Annual rate of exacerbation	Reduction in annual exacerbation in patients who received high-dose benralizumab, improvement in FEV1 and ACQ-6 scores in those who received any dose
Dupilumab					
Wenzel NEJM 2013 [61]	Adults with peripheral blood eosinophil count ≥300 cells/μL or induced sputum eosinophil count ≥3% with ACQ-5 score 1.5–3 despite ICS and LABA therapy	104	12 study period, 8 follow-up (20 total)	Occurrence of exacerbation within 12 weeks	Reduction in number of exacerbations, improvement in FEV1, improved morning and evening peak expiratory flow, improvement in ACQ-5 score

Table 2 continued

Trial	Study population	Size (number of subjects)	Duration (weeks)	Primary outcome	Results
Lebrikizumab					
Corren NEJM 2011 [66]	Adults with FEV1 40–80% predicted, airway reversibility, and ACQ-5 score ≥1.5 despite ICS therapy and uncontrolled symptoms	219	24 study period, 8 follow-up (32 total)	Change in baseline FEV1 at week 12	Improvement in FEV1 in those with a high periostin level (cutoff value not provided), no change in ACQ-5 score or exacerbation rate
Hanania Thorax 2015 [67]	Adults with FEV1 40–80% predicted, airway reversibility, and ACQ-5 score ≥1.5 despite ICS therapy, a second controller, and uncontrolled symptoms	463	52	Rate of exacerbation at 52 weeks	Reduction in number of exacerbations in all treatment groups and improvement in FEV1 in those with high systemic periostin (≥50 ng/mL); no change in AQLQ, peak expiratory flow, or SABA use

AJRCM: American Journal of Respiratory and Critical Care Medicine, *NEJM: The New England Journal of Medicine*, *AJEM: American Journal of Emergency Medicine*, *ICS* inhaled corticosteroid, *ACQ* asthma control questionnaire, *LABA* long-acting beta agonist, *AQLQ* asthma quality of life questionnaire, *JACQ* Juniper asthma control questionnaire, *FEV1* forced expiratory volume in one second, *FVC* forced vital capacity, $FEF_{25-75\%}$ forced expiratory flow between 25% and 75% of forced vital capacity, *SABA* short-acting beta agonist

samples defined by a sputum eosinophil count of 3% or greater at least once in the previous two years despite high-dose (either inhaled or systemic) corticosteroid therapy, and recurrent exacerbations. Over the 50-week trial period, there was a significant reduction in total number and rate of exacerbations [relative risk, 0.57; 95% confidence interval (CI), 0.32–0.92; $p = 0.02$], as well as a modest improvement in the Asthma Quality of Life Questionnaire (AQLQ) score (mean improvement in AQLQ 0.55 (minimal clinically important difference 0.5 [39])). However, there was no effect on asthma symptoms or forced expiratory volume in one second (FEV_1), suggesting that these markers of disease may be improved through other mechanisms. The only serious adverse events reported were hospitalizations for severe asthma (10% mepolizumab vs. 34% placebo).

A follow-up report by the same authors 12 months after trial completion included the majority (56 of 61) of subjects included in the original study [40]. After cessation of mepolizumab, participants experienced significant increases in peripheral blood and sputum eosinophil counts as soon as three months after trial completion, followed by an increase in exacerbation frequency and worsening asthma control as noted by the Juniper Asthma Control Questionnaire (JACQ). The increase in both peripheral blood and sputum eosinophils preceding the increase in rate of

exacerbations suggests a relationship between eosinophilic inflammation and asthma control.

In a similar cohort of patients, Nair et al. showed an association between intravenous mepolizumab administration and overall reduction in daily prednisone dose [35] in a smaller, proof of concept study. Twenty adult patients who required daily treatment with oral prednisone and high-dose inhaled glucocorticoids (600–2000 μg of fluticasone or equivalent) to control symptoms and had persistent sputum eosinophilia with a least 3% of cells in an induced sputum sample were randomized to either mepolizumab 750 mg or placebo IV every four weeks for 26 weeks. Administration of mepolizumab resulted in fewer exacerbations, a longer time to first exacerbation, and a significant reduction in prednisone requirements. Subjects treated with mepolizumab were able to reduce their dose of prednisone by a mean (±SD) of 83.8 ± 33.4% of the maximum possible dose compared to 47.7 ± 40.5% in the placebo group ($p = 0.04$), but there was no difference in the perhaps more clinically meaningful final mean dose of prednisone between the groups. There were no serious adverse events in the study.

In the first of two large international multicenter, randomized, double-blinded, placebo-controlled trials, the Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) trial [36], Pavord et al. enrolled 621 participants with severe asthma with recurrent exacerbations and evidence of eosinophilic inflammation defined as a sputum eosinophil count ≥3%, peripheral blood eosinophil count ≥300 cells/μL, exhaled nitric oxide concentration (FeNo) of at least 50 ppb, or "prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or oral corticosteroids." Participants were randomized to one of three doses of mepolizumab (75, 250, or 750 mg) or placebo IV every four weeks for 13 infusions. The investigators found that, over the course of 52 weeks, intravenous mepolizumab reduced peripheral blood and, to a lesser degree, sputum eosinophil counts, and reduced the rate of clinically significant exacerbations at a similar rate regardless of dose when compared to placebo. Similar to previous studies [33–35], there was no difference between the groups in asthma control questionnaire (ACQ) scores or FEV_1, suggesting that strategies for managing exacerbations and these other aspects of control might be considered differently in this population. A subgroup analysis indicated that the efficacy of mepolizumab in reducing exacerbation rates increased with higher baseline eosinophil counts and number of exacerbations within the preceding year but not baseline FeNo, suggesting that careful phenotyping in patient selection for use of this agent will be important in future studies. The broad definition of eosinophilic inflammation for the entry criteria for this study may have limited its ability to show significant change, but the idea of noninvasive, clinically available markers is appealing.

The second large randomized, double-blind, placebo-controlled trial, the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study [37], evaluated a similar population of refractory asthma with recurrent exacerbations, but included the subcutaneous (SQ) route of administration as an intervention arm, and tightened the definition of eosinophilic inflammation to include only those subjects with peripheral blood eosinophil counts of at least 150 cells/μL at screening or 300 cells/μL at some point in the previous year. Participants were randomized to mepolizumab administered 75 mg IV or 100 mg

SQ or placebo every four weeks for 32 weeks. Both routes of administration had similar efficacies. When compared to placebo, those treated with mepolizumab demonstrated an improvement in lung function, had evidence of improved asthma control with a lower ACQ-5 score (although less than the minimal clinically significant change of 0.5 [39]), and had significant improvement in quality of life (QOL) as measured by a numerical decrease on the St. Georges Respiratory Questionnaire (SGRQ). Mepolizumab reduced overall exacerbation rates from 1.74 to 0.93 exacerbations per patient year in the IV group (47% reduction, 95% CI 28–60%; $p < 0.001$) and 0.83 in the SQ group (53% reduction, 95% CI 36–65%; $p < 0.001$). Efficacy was again noted to be linked with markers of eosinophilic inflammation, with those subjects with peripheral blood eosinophil counts of over 500 cells/μL having the greatest reduction in exacerbations. The most commonly reported adverse events were injection-site reactions. This study further supports the notion that, with careful patient selection, mepolizumab can be effective in a specific population of patients with severe eosinophilic asthma.

This early suggestion that mepolizumab could be useful as a glucocorticoid-sparing agent [35] was later confirmed by the larger Steroid Reduction with Mepolizumab Study (SIRIUS) [41], in which 135 patients with glucocorticoid-dependent eosinophilic asthma were randomized to mepolizumab 100 mg SQ or placebo every four weeks for 20 weeks as an additive therapy. Similar to MENSA [37], the SIRIUS investigators defined eosinophilic asthma as the presence of a peripheral blood eosinophil level of least 300 cells/μL on initial screening, or at least 150 cells/μL during the run-in phase of the trial. Administration of mepolizumab resulted in a significant reduction in daily glucocorticoid dose (50% median reduction from baseline compared to no reduction in the placebo group, $p = 0.007$), a reduced annualized rate of exacerbation (1.44 exacerbations per patient year versus 2.12, $p = 0.04$), as well as improvements in the ACQ-5 and SGRQ. Previous studies [34, 36, 37] did not demonstrate this improvement in asthma control with mepolizumab, suggesting that there may be a greater potential for symptomatic control in those patients who are steroid dependent. There was no significant difference in ability to wean completely off glucocorticoid therapy, but the trial's short length may have limited the ability to completely assess this or its long-term effect on exacerbations. The safety profile for mepolizumab was similar to placebo, but six (4%) participants in the two study groups developed non-neutralizing antibodies to mepolizumab.

Overall, a 2013 meta-analysis of seven randomized controlled trials comparing mepolizumab to placebo concluded that mepolizumab "appears to be useful for control of exacerbations and improve asthma-related quality of life in individuals with persistent airway eosinophilia" [42]. The authors did not find a significant difference in pooled change in FEV_1 [42], although the analysis was published prior to the MENSA study, so additional statistical analysis may be warranted in the future. The reductions in both peripheral [33–36, 42] and sputum [34, 35, 42] eosinophil counts in those receiving mepolizumab were significant and, given the specificity of monoclonal-antibody-targeted therapy, is supportive of the causal relationship between reduction in eosinophilic inflammation and rate of exacerbation.

Based on the growing body of literature [33–37, 41, 42], mepolizumab was approved

for clinical use in the European Union by the European Medicines Agency (EMA) on September 24, 2015 [43], and in the United States by the Food and Drug Administration (FDA) on November 4, 2015 [44]. It is approved as an add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype (peripheral blood eosinophil count ≥300 cells/μL or sputum eosinophil count ≥3%) aged 12 years and older. The recommended dose is 100 mg administered by subcutaneous injection of the thigh, upper arm, or abdomen every four weeks. There were few serious side effects reported in clinical trials of mepolizumab [44]. The most common adverse effect was headache (19% vs. 18% placebo), followed by injection site reaction (8% vs. 3% placebo). Severe hypersensitivity reactions have been reported in pooled data (7% of those who received placebo versus 10% who received mepolizumab), as has herpes zoster infection (two cases during clinical trials) [44].

RESLIZUMAB

Similar to mepolizumab, reslizumab is a humanized monoclonal antibody targeted against IL-5, preventing binding to eosinophil targets [45]. Several randomized controlled trials comparing reslizumab to placebo have been completed. The first enrolled 106 adults with poorly controlled eosinophilic asthma defined as ≥3% eosinophils on induced sputum and an ACQ-7 score of 1.5 or higher despite high-dose inhaled corticosteroid therapy (at least 880 μg fluticasone or equivalent daily) plus an additional controller [46]. Over a short 15-week observation period, there was a trend towards improvement in mean ACQ-7 score with reslizumab administration, but this did not reach statistical significance except in the subgroup of participants with nasal polyps ($p = 0.0119$). Participants who received reslizumab showed significantly greater improvements in lung function, including FEV_1 and forced vital capacity (FVC), and reductions in both peripheral blood (40% reduction) and induced sputum (95% reduction) eosinophil counts than those who received placebo. The improvement in FEV_1 was most pronounced in those subjects with peripheral blood eosinophils of at least 500 cells/μL or more at baseline, further highlighting the need to clearly establish the appropriate phenotype in which these agents are likely to be effective.

A more recent publication described data collected from two duplicate multicenter, randomized, placebo-controlled trials that included adolescents and adults with uncontrolled eosinophilic asthma defined by an ACQ-7 score ≥1.5 and at least 440 μg fluticasone or equivalent daily with or without an additional controller agent and with a peripheral blood eosinophil count ≥400 cells/μL. A total of 953 participants were randomized to receive either reslizumab 3 mg/kg or placebo IV every four weeks for one year. In pooled data from both trials, those who received reslizumab had a significant improvement in overall exacerbation rates to 0.84 exacerbations per patient per year versus 1.81 in the placebo group (reduction of 54%). Reslizumab treatment also improved lung function, AQLQ scores (improvement of 1.08 versus 0.81 in those who received placebo) and ACQ-7 scores (reduction of 1.02 versus 0.77 in those who received placebo) over the 52-week study period. While reslizumab had a similar effect on rates of asthma exacerbation as those reported for mepolizumab in DREAM [36] and MENSA [37], the improvements in asthma control and lung function were more notable. The authors speculate that the higher

eosinophil threshold of ≥400 cells/μL for inclusion in these studies may more accurately represent airway eosinophilia [47], and may ultimately better predict which patients will respond to inhibition of IL-5. With the exception of two patients who suffered from anaphylaxis that was believed to be related to the study medication, adverse events were similar in the two groups [48].

A confirmatory trial comparing two doses of reslizumab [49] in patients with poorly controlled eosinophilic asthma (blood eosinophils ≥400 cells/μL) randomized patients 1:1:1 to 0.3 mg/kg reslizumab, 3 mg/kg reslizumab, and placebo administered IV once every four weeks for 16 weeks. Reslizumab improved lung function, asthma symptoms, and quality of life when compared to placebo, but there was no significant difference in asthma control. The effect was generally greater at the 3.0 mg/kg dose, without an increase in adverse events. The improvement in FEV_1 did not correlate with baseline eosinophil levels of ≥400 cells/μL [49]. Finally, Corren et al. evaluated the effect of reslizumab in a population of adults with inadequately controlled asthma unselected for eosinophilia [50]. When compared to placebo, there was no difference in FEV_1, ACQ scores, or rescue inhaler use between groups. The study was not powered for detailed subgroup analyses, but in those participants with a peripheral blood eosinophil count of ≥400 cells/μL, there was a significant improvement in FEV_1 (270 mL) compared to placebo, supporting a blood eosinophil threshold of ≥400 cells/μL for clinical use.

Based on the previous body of work [46, 48–50], reslizumab was approved for use in the US on March 23, 2016 by the FDA [51] and the EU on June 23, 2016 by the EMA [52] for add-on maintenance therapy for severe asthma in adults aged 18 years or older with an eosinophilic phenotype. The recommended dose is 3 mg/kg every four weeks administered by intravenous infusion over 20–50 min [53]. Anaphylaxis was reported in 0.3% of patients included in all clinical trials (0% in placebo). Other adverse effects include oropharyngeal pain (2.6% vs. 2.2% placebo) and creatine phosphokinase (CPK) elevation (14% vs. 9% placebo) [53].

BENRALIZUMAB

Rather than directly binding and inhibiting IL-5, benralizumab is an investigational humanized monoclonal antibody that is directed at a subunit of the IL-5 receptor (IL-5R) located on eosinophils and basophils that induces apoptosis [54]. In a small phase-one trial, intravenous and subcutaneous benralizumab was shown to effectively decrease eosinophil counts in both peripheral blood and sputum, with a trend toward a reduction in peripheral blood basophil counts compared to placebo [55]. In a phase two, randomized, double-blind, placebo-controlled parallel group study, patients with physician-diagnosed asthma and at least one exacerbation requiring urgent care in the preceding 12 months who presented to the emergency department with an acute asthma exacerbation were randomized to either a single dose of benralizumab (0.3 or 1.0 mg/kg) or placebo in addition to usual care administered at the time of presentation, and were followed over a 12-week period [56]. Patients were enrolled regardless of peripheral blood eosinophil levels. There was no difference between groups in number of exacerbations at four, 12, or 24 weeks, FEV_1, ACQ, or AQLQ scores. However, pooled analysis found that benralizumab significantly decreased the rate of exacerbations when compared to placebo ($p = 0.01$). Interestingly, the effect of

benralizumab was not related to blood eosinophil count in this study.

A second larger randomized, controlled, dose-ranging trial enrolled adults with uncontrolled moderate-to-severe asthma and a history of recurrent exacerbations to receive benralizumab over one year at varying doses [57]. Patients were classified as either eosinophilic or non-eosinophilic based on an elevated FeNo (>50 ppb) in combination with a mathematical algorithm to predict sputum eosinophils. A significant reduction in annual exacerbation rate was found in those subjects with an eosinophilic subtype who received 100 mg benralizumab versus those who received placebo, although, due to the nature and goals of the study, the authors accepted $p < 0.169$ as significant rather than the traditional 0.05. Additionally, there were significant improvements in FEV_1 and ACQ-6 scores in all subjects, regardless of phenotype, who received benralizumab compared to those who did not. The activity in the non-eosinophilic subtype suggests that benralizumab may be active towards other IL-5R-expressing cells that contribute to inflammation [57].

DUPILUMAB

Dupilumab is an investigational humanized monoclonal antibody against the IL-4 receptor α-subunit present in two distinct receptors on lymphocytes (type I receptor) and bone marrow precursors (type II receptors) [27, 58–60]. The type I receptor present on lymphocytic precursors is predominantly responsible for Th2 cell differentiation and maturation [27, 60], so inhibition of this differentiation should reduce the downstream effects of eosinophilic maturation and activation. A phase-two randomized controlled trial [61] enrolled 104 adults with uncontrolled moderate-to-severe eosinophilic asthma (peripheral blood eosinophil count ≥300 cells/μL or induced sputum eosinophil count ≥3%). Participants were randomized to receive subcutaneous dupilumab 300 mg weekly or placebo over 12 weeks in addition to inhaled fluticasone and salmeterol. After 4 weeks, participants were advised to discontinue salmeterol and tapered off fluticasone. Compared to placebo, dupilumab significantly reduced the number of exacerbations over the study period (odds ratio 0.08; 95% CI, 0.02–0.28; $p < 0.001$), despite discontinuation of inhaled corticosteroid and long-acting beta-agonist therapy. Dupilumab also resulted in improved lung function and asthma control, but the short length of the study did not allow the investigators to duplicate clinical practices [61]. Although dupilumab effectively reduced FeNo, serum IgE, and other serum biomarkers supporting biologic activity, there was no change in peripheral blood eosinophil counts, suggesting that reducing eosinophils is not essential for reducing disease activity.

LEBRIKIZUMAB

Interleukin-13 (IL-13) is a pro-inflammatory Th2 cytokine secreted by activated T-cells, eosinophils, natural killer cells, mast cells, and basophils that acts as a potent stimulator of mucus production, airway fibrotic changes, and airway eosinophilia [62]. Serum levels are elevated in asthma, and this is thought to be a mechanism of steroid resistance [63]. One of the mechanisms by which IL-13 induces airway fibrosis and remodeling is by upregulating the secretion of periostin [64], which has been linked as a systemic biomarker specific for airway eosinophilia [65]. Lebrikizumab is a

humanized monoclonal antibody that binds to IL-13, which is under investigation for the treatment of uncontrolled asthma [66, 67]. Early studies indicate that lebrikizumab may improve lung function (percent improvement in baseline FEV_1 compared to placebo ranged from 8.2% to 10.7% in three phase-two trials [66, 67], although this improvement seems to be limited to those patients with high baseline levels of systemic periostin ($\geq$50 ng/mL). In secondary analysis, lebrikizumab was also shown to decrease FeNo, another marker of eosinophilic airway inflammation [68].

CONCLUSION

Asthma is a complex chronic inflammatory condition where patients with severe eosinophilic airway disease pose a particular challenge for clinicians. As new biologic therapies targeted at specific subtypes of asthma become available, it will be increasingly important to be able to readily identify those subgroups of patients who will be the most likely to respond. Our concept of asthma phenotyping has evolved from emphasizing broad clinical classifications to much more specific biologic characteristics that can more clearly link the underlying pathology to the phenotype.

The place of these new biologic agents in our armamentarium of options for patients with uncontrolled disease is still being defined, but the decision to begin such therapies should carefully weigh the cost of the agent, its safety profile, and the target population. Standard asthma therapies should be optimized according to national guidelines [69, 70], with attention paid to adherence and control of comorbid conditions before the addition of biologics. For currently approved therapies [44, 53], we recommend consideration prior to the initiation of chronic systemic steroids to reduce the risk of exacerbations, or to use them in add-on therapies as potential steroid-sparing agents. While strategies for long-term monitoring of these agents have not been defined, we recommend a year-long trial for those patients who tolerate the medications, with the monitoring of frequency of exacerbations and healthcare utilization, the assessment of asthma control with standardized questionnaires, and the ability to wean systemic corticosteroids as primary goals.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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